

# No Association between Gastroesophageal Reflux and Cancers of the Larynx and Pharynx

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## Abstract

**Purpose:** To examine the proposed relation between gastroesophageal reflux disease and cancers of the larynx and pharynx.

**Experimental Design:** A cohort of 66,965 patients with discharge diagnoses of heartburn, hiatal hernia, or esophagitis was identified in the Swedish Inpatient Register. We observed a total of 376,622 person-years in the cohort. Identification of laryngeal and pharyngeal cancers was achieved through the Swedish Cancer Register. Standardized incidence ratios, the ratio of the observed to the expected number of cancers, derived from the general Swedish population and adjusted for sex, age, and calendar year, was used to estimate the relative risk.

**Results:** During follow-up, 30 cases of laryngeal and 31 cases of pharyngeal cancer were detected in the cohort. Slightly

increased risks of laryngeal [relative risk, 1.6; 95% confidence interval (CI), 1.1-2.2] and pharyngeal carcinomas (relative risk, 1.9; 95% CI, 1.3-2.8) were observed in the total reflux cohort. After stratification to exclude cohort members with a diagnosis of alcoholism, no significant increase in the risk of laryngeal (relative risk, 1.3; 95% CI, 0.8-2.0) or pharyngeal carcinomas (relative risk, 1.0; 95% CI, 0.5-1.6) was found compared with the general population. Furthermore, there were no dose-response patterns of the risk for laryngeal and pharyngeal cancers with years of cohort follow-up, indicators of reflux severity, or specificity of reflux diagnosis.

**Conclusion:** This study provides no evidence in support of the proposed association between gastroesophageal reflux disease and cancers of the larynx or pharynx. (Cancer Epidemiol Biomarkers Prev 2005;14(5):1194-7)

## Introduction

In Europe and North America, laryngeal and pharyngeal cancers together constitute between 30% and 50% of all diagnosed malignant tumors in the head and neck area (1-3). Both cancers are aggressive with a 5-year relative survival rate of approximately 60% for laryngeal cancer and 30% for pharyngeal cancer (4). The use of tobacco and alcohol are the only well-established risk factors for these tumors (2, 5, 6).

Gastroesophageal reflux disease, one of the most prevalent health disorders in the Western world (7-9), is strongly associated with adenocarcinoma of the esophagus (5, 10-12), which stands in sharp contrast to the lack of association between reflux and squamous cell carcinoma of the esophagus (5, 10). A link between gastroesophageal reflux and laryngeal and pharyngeal cancers has also been suggested, based on results from several case series (13-17). Recently, a 2-fold increased risk for each of these two tumors was found among persons with a history of gastroesophageal reflux disease in a nested case-control study conducted using the computerized database of veterans' hospitals across the United States (18). However, the reported association with reflux is enigmatic, because >90% of laryngeal and pharyngeal cancers are of the squamous cell type (2, 6) and the available evidence from studies of esophageal squamous cell carcinoma does not support a link with gastroesophageal reflux disease (10, 11).

To evaluate the relation between gastroesophageal reflux disease and the risk of laryngeal and pharyngeal cancer, we conducted a nationwide population-based cohort study among patients hospitalized for gastroesophageal reflux disease in Sweden between 1965 and 1997.

## Materials and Methods

A detailed description of the methods used in this large, retrospective cohort study has been described elsewhere (5). In brief, we used data from the Swedish Inpatient Register, a register that was established in 1964 to 1965, in which discharge diagnoses, current surgical procedures, and the patients' unique national registration numbers were computerized for each hospitalization. The coverage of the Inpatient Register was 60% in 1969, 85% in 1983, and included all Swedish hospitals from 1987 and thereafter. From 1965 to 1997, we identified 85,526 unique national registration numbers with at least one in-hospital episode with a discharge diagnosis representing gastroesophageal reflux. Of these, 13,198 had also been treated with anti-reflux surgery. By follow-up using national registration numbers, we could ascertain deaths and emigrations through record linkage to the nationwide Registry of Causes of Death and the Emigration Registry for information on dates of death or emigration. Incidence of cancer was identified through linkage to the Swedish National Cancer Register, which was estimated to be >98% complete (19). Linkage to the Registers of the Total Population, Death, and Emigration identified 169 records with national registration numbers that did not match any living, dead, or emigrated person, and were therefore excluded. Also excluded were 2,455 records with inconsistent or invalid dates found during the record linkage, and 7,720 records with prevalent cancers. The 8,217 patients whose diagnosis of reflux occurred at the same time of or after anti-reflux surgery were excluded from the main analysis because we considered the exposure to

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gastroesophageal reflux to have ended after anti-reflux surgery. Person-time occurring between a diagnosis of reflux and anti-reflux surgery was included in the study. We also did additional analyses including these 8,217 patients, however, to address the concern that the carcinogenic process might have already been initiated before anti-reflux surgery.

The regional research ethics committee in Stockholm, Sweden approved the study.

**Statistical Analysis.** In the reflux cohort, person-time was calculated from the date of the first recorded hospital discharge with a diagnosis of heartburn, hiatal hernia, or esophagitis until the date of the first occurrence of any cancer, anti-reflux surgery, death, emigration, or the end of observation (December 31, 1997), whichever occurred first. If any patient had more than one type of reflux diagnosis, they were prioritized in the following order: (a) esophagitis, (b) hiatal hernia, and/or (c) heartburn. Cancers found incidentally first at autopsy were excluded from the analyses to avoid ascertainment bias. Because the likelihood of being hospitalized with a reflux-related diagnosis may increase due to insidious symptoms of a yet undetected cancer, we excluded all cancers and person-years accrued during the first year of follow-up in the cohort. The standardized incidence ratio (SIR), the ratio of the observed to the expected number of cancers, was used to calculate relative risk. The expected number of cancers occurring in the entire Swedish population was calculated by multiplying the observed person-time by age- (in 5-year groups), gender-, and calendar year-specific cancer incidence rates. The SIRs are inherently adjusted for confounding by age at follow-up, gender, and calendar year. Confidence intervals of SIRs were calculated assuming that the observed number of events followed a Poisson distribution (20). To minimize the potential confounding effect from alcohol exposure, we did additional analyses excluding patients with a diagnosis of alcoholism ( $n = 5,699$ ).

## Results

The final reflux cohort included 66,965 patients contributing to a total of 376,622 person-years of follow-up. The general characteristics of the cohort are shown in Table 1. During the first year, we identified six cases of laryngeal carcinoma [relative risk, 1.7; 95% confidence interval (CI), 0.6-3.7] and three cases of pharyngeal carcinoma (relative risk, 1.0; 95% CI, 0.2-3.0). These cancers and person-years were excluded from further analysis.

After exclusion of the first year of observation, the risk of laryngeal carcinoma was significantly elevated by 60% among members of the reflux cohort compared with that of the general population (relative risk, 1.6; 95% CI, 1.1-2.2; Table 2).

**Table 1. Characteristics of the gastroesophageal reflux disease cohort**

	<i>n</i> (%) or mean $\pm$ SD
Number of patients	66,965
Female sex	31,691 (47.3)
Age at entry	63.0 $\pm$ 18.7
Type of reflux disease	
Heartburn	781 (1.2)
Hiatal hernia	21,287 (31.8)
Esophagitis	44,897 (67.0)
Diagnosis of alcoholism	5,699 (8.5)
Anti-reflux surgery*	4,981 (7.4)
Reflux as primary diagnosis	36,802 (55.0)

\*An additional 8,217 patients who were diagnosed to have reflux after anti-reflux surgery were excluded from the main analyses.

The excess risk was observed mainly within the first 4 years of follow-up. After exclusion of 5,699 cohort members with a diagnosis of alcoholism, the excess risk was no longer statistically significant (relative risk, 1.3; 95% CI, 0.8-2.0). The result was similar when we included the 8,217 patients who were diagnosed with gastroesophageal reflux disease at the time of anti-reflux surgery or thereafter (relative risk, 1.3; 95% CI, 0.9-2.0).

The risk of pharyngeal carcinoma was elevated nearly 2-fold in the overall reflux cohort (relative risk, 1.9; 95% CI, 1.3-2.8), after excluding the first year of observation (Table 2). The point estimates for the risk of pharyngeal carcinoma increased further with increasing years of follow-up. After excluding those with a diagnosis of alcoholism, the risk was reduced to unity (relative risk, 1.0; 95% CI, 0.5-1.6) and did not maintain a dose-response pattern with years of follow-up. Including the 8,217 patients who received their reflux diagnosis at the time of anti-reflux surgery or thereafter in the analysis did not change the estimate substantially (relative risk, 0.8; 95% CI, 0.5-1.4).

Risk for laryngeal carcinoma generally did not show patterns of greater excess risks with indicators of increased diagnostic specificity and severity, i.e., reflux diagnosis in specialized hospital departments, diagnosis verified by endoscopy, reflux disease being the primary diagnosis, or hospital admission as an emergency case (Table 3). There was, however, a >2-fold excess risk among those with a diagnosis of hiatal hernia at entry even after excluding those with alcoholism. Detailed analysis by follow-up duration in this subgroup revealed that the excess risk was confined to the first 4 years of follow-up only (relative risk during 1-4 years of follow-up, 4.0; 95% CI, 2.2-6.7; and relative risk from 5 years or longer follow-up, 1.1; 95% CI, 0.4-2.6). In the overall cohort, the risk of pharyngeal carcinoma appeared to increase with greater diagnostic specificity or severity of reflux disease. However, the excess risks diminished when persons diagnosed with alcoholism were excluded (Table 3). None of the 61 cases of laryngeal or pharyngeal carcinomas was adenocarcinoma.

The risks for lung cancer (relative risk, 1.2; 95% CI, 1.0-1.3) and urinary bladder cancer (relative risk, 1.1; 95% CI, 0.9-1.2), malignancies that are strongly linked with tobacco use, were slightly increased in the reflux cohort compared with the general Swedish population.

## Discussion

In the present study, we observed increased risks of subsequent cancers of the larynx and pharynx among persons who were admitted for in-patient care with discharge diagnoses of heartburn, hiatal hernia, or esophagitis. This excess risk was attenuated, with no statistically significant increase in risk remaining, after exclusion of persons who had a recorded diagnosis of alcoholism, indicating that the associations were mostly due to confounding from alcohol exposure. Moreover, indicators of increasing severity and diagnostic specificity of reflux disease did not reveal any dose-response relations with the risks of these tumors. Hence, no true association between reflux disease and cancers of the larynx or pharynx was found in our study.

A major strength of our study is the population-based design with essentially complete follow-up of cohort members through linkage to the nationwide Cancer Register and Death and Emigration Registers. This design minimizes potential selection bias and incomplete follow-up of cases that may occur in studies based on hospital series or selected populations. Recall bias is avoided in our study by using recorded history of reflux disease. In addition, the relatively large cohort size reduces the influence of chance or random error.

**Table 2. Relative risks and 95% CI for cancers of the larynx and pharynx in patients with heartburn, hiatal hernia, or esophagitis in total and according to sex and follow-up duration, including stratification for patients without alcoholism**

Characteristics	Total		Without alcoholism	
	Laryngeal carcinoma	Pharyngeal carcinoma	Laryngeal carcinoma	Pharyngeal carcinoma
	Number of cases, relative risk* (95% CI)			
Total	30, 1.6 (1.1-2.2)	31, 1.9 (1.3-2.8)	23, 1.3 (0.8-2.0)	14, 1.0 (0.5-1.6)
Sex				
Male	25, 1.4 (0.9-2.1)	25, 2.1 (1.4-3.1)	18, 1.2 (0.7-1.8)	9, 0.9 (0.4-1.6)
Female	5, 2.7 (0.9-6.3)	6, 1.5 (0.5-3.2)	5, 2.7 (0.9-6.4)	5, 1.3 (0.4-2.9)
Follow-up				
1-4 y	18, 1.9 (1.1-3.0)	11, 1.4 (0.7-2.5)	17, 2.0 (1.1-3.1)	7, 1.0 (0.4-2.0)
5-9 y	8, 1.4 (0.6-2.7)	12, 2.4 (1.3-4.2)	3, 0.6 (0.1-1.6)	4, 0.9 (0.2-2.3)
≥10 y	4, 1.1 (0.3-2.7)	8, 2.5 (1.1-5.0)	3, 0.9 (0.2-2.6)	3, 1.1 (0.2-3.1)

\*Relative risks were calculated as SIRs.

A potential weakness of the study is that data on smoking, a well-established risk factor for laryngeal and pharyngeal cancers (2, 5, 6) was not available for adjustment. However, the stratification to exclude cohort members with a diagnosis of alcoholism, representing the extreme in alcohol exposure, also adjusts for confounding from smoking to some extent because there is a strong connection between habits of smoking and drinking alcohol (21, 22). To further estimate the extent of tobacco exposure in the reflux cohort, we analyzed the risks of subsequent lung cancer and urinary bladder cancer, two tumors that are closely linked to tobacco smoking. The point estimates for the relative risks for both these cancers were slightly elevated, suggesting that smokers may be slightly overrepresented in the cohort and that smoking may positively confound the risk of laryngeal or pharyngeal carcinomas in our cohort. Therefore, the true relative risks may be even lower than the risk shown after exclusion of alcoholics only, thus further challenging the possibility of a positive association between gastroesophageal reflux and cancers of the larynx and pharynx.

It is likely that a proportion of the general Swedish population who suffered from gastroesophageal reflux disease were not hospitalized, and hence, were not included in the study cohort. It is also possible that a small proportion of the patients in the reflux hospitalized cohort may not have had gastroesophageal reflux disease. However, the proportion of

the general population with reflux disease is likely to be small compared with the proportion of persons with reflux disease in the hospitalized cohort. Moreover, the severity of the reflux disease in the cohort is likely to be high in comparison with the subgroup of persons in the general population with reflux disease who have not been hospitalized because hospitalization is reserved for severe manifestations. Therefore, it is unlikely that the potential misclassification of subjects substantially affected our findings. To the extent that some individuals with mild reflux disease might not have been included in the cohort, our results can only be generalized for patients with severe reflux disease relative to the general population.

Despite the cohort size of 66,965 persons and follow-up of 376,622 person-years, relatively few cases of laryngeal and pharyngeal cancer were detected in the cohort due to the low incidence of these cancers in the source population. This may somewhat limit the statistical power of the study, although confidence intervals, despite this, are fairly narrow in most analyses.

The diagnosis of erosive esophagitis represents true gastroesophageal reflux with very high specificity as it is an effect of peptic injury to the esophageal mucosa, and very rarely caused by anything other than reflux. Hiatal hernia is an anatomic alteration strongly associated with reflux, although also prevalent among persons without reflux, thus

**Table 3. SIRs and 95% CIs for cancers of the larynx and pharynx in patients with heartburn, hiatal hernia, or esophagitis according to indicators of severity and specificity of diagnosis**

Characteristics	Total		Without alcoholism	
	Laryngeal carcinoma	Pharyngeal Carcinoma	Laryngeal carcinoma	Pharyngeal carcinoma
	Number of cases, relative risk* (95% CI)			
Diagnosis				
Heartburn	0, — (—)	0, — (—)	0, — (—)	0, — (—)
Hiatal hernia	20, 2.3 (1.4-3.6)	9, 1.2 (0.6-2.3)	19, 2.4 (1.4-3.7)	3, 0.4 (0.1-1.3)
Esophagitis	10, 1.0 (0.5-1.8)	22, 2.6 (1.6-3.9)	4, 0.4 (0.1-1.1)	11, 1.5 (0.7-2.6)
Diagnosed in Otolaryngology or Surgery Department				
Yes	16, 1.5 (0.8-2.4)	22, 2.5 (1.6-3.8)	10, 1.0 (0.5-1.9)	9, 1.1 (0.5-2.1)
No	14, 1.7 (0.9-2.8)	9, 1.3 (0.6-2.4)	13, 1.7 (0.9-2.9)	5, 0.8 (0.3-1.8)
Diagnosis by endoscopy				
Yes	10, 1.4 (0.7-2.6)	14, 2.5 (1.3-4.1)	6, 1.0 (0.4-2.1)	4, 0.8 (0.2 -2.0)
No	20, 1.6 (1.0-2.5)	17, 1.7 (1.0-2.6)	17, 1.5 (0.9-2.4)	10, 1.1 (0.5-1.9)
Reflux as primary or non-primary diagnosis				
Never primary diagnosis	18, 2.3 (1.3-3.6)	9, 1.4 (0.6-2.6)	15, 2.1 (1.2-3.4)	5, 0.8 (0.3-1.9)
Primary reflux diagnosis	12, 1.1 (0.6-1.9)	22, 2.4 (1.5-3.6)	8, 0.8 (0.3-1.5)	9, 1.1 (0.5-2.0)
Never admitted as emergency case	4, 0.8 (0.2-2.4)	8, 2.0 (0.9-4.0)	2, 0.5 (0.1-1.6)	4, 1.1 (0.3-2.8)
Admitted as emergency case	8, 1.2 (0.5-2.4)	14, 2.6 (1.4-4.3)	6, 1.1 (0.4-2.3)	5, 1.1 (0.3-2.5)

\*Relative risks were calculated as SIRs.

representing reflux with a lower degree of specificity compared with esophagitis. As the classification of cohort members by type of reflux diagnosis was done in order to examine whether associations between reflux diagnoses and the cancers studied were affected by the specificity of reflux diagnosis, we prioritized esophagitis over hiatal hernia in order to sharpen the steps in terms of specificity. Overlap of these two diagnoses was actually not common. A separate analysis including all hiatal hernia patients, irrespective of esophagitis diagnosis, revealed similar relative risks (21 laryngeal carcinoma, SIR = 2.2; 95% CI, 1.4-3.4; 10 pharyngeal carcinoma, SIR = 1.2; 95% CI, 0.6-2.3). For cohort members with hiatal hernia without esophagitis, there was a significant >2-fold increase in the risk of laryngeal cancer even after the exclusion of cohort members with a diagnosis of alcoholism. The excess risk leveled off after 5 years, however, indicating that this finding might be due to surveillance bias.

In 1976, it was first suggested that inflammatory disease could cause laryngeal cancer (23), and in the late 1980s, it was further proposed that gastroesophageal reflux could play a causal role in laryngeal and pharyngeal carcinogenesis (14, 17). Until recently, the only available data on this subject were from uncontrolled case series, of which some authors interpreted their data in favor of an association (13-17), others against (24). In 2001, the first controlled study addressing this issue was published in the form of a nested case-control study in the United States, demonstrating a moderately strong association between reflux-related inpatient discharge diagnoses and cancers both of the larynx and pharynx (18). A source of potential bias in this study is differential patterns of admission to the Veterans Affairs Hospitals for cancer cases and controls. For instance, if patients with gastroesophageal reflux disease are more likely to stay in the Veterans Affairs Hospital system for treatment, hence may have a greater chance of being diagnosed with cancer, it may positively bias the association between reflux disease and cancer. Moreover, the minimum time between the assessment of reflux exposure and end point cancer diagnosis was only 1 month in that study, which in our view is too short and might leave the door open for reversed causality and selection bias.

Gastroesophageal reflux is known to be a strong risk factor for adenocarcinoma of the esophagus, but not a risk factor for squamous cell carcinoma of the esophagus (11). Cancers of the larynx and pharynx are almost exclusively of the squamous cell histologic type (2, 6). Because the larynx and pharynx are less exposed to gastroesophageal reflux than the esophagus, it is biologically unlikely, in our view, that gastroesophageal reflux would increase the risk of squamous cell carcinoma of the larynx and pharynx.

In conclusion, the findings of this study do not support the presence of a causal association between gastroesophageal reflux disease and cancers of the larynx and pharynx.

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